Sub D3 18. (Amended) A method for detecting a mammalian target neoplastic nucleic acid having a mutant nucleotide sequence in a tissue specimen which is external to a primary neoplasm, comprising extracting [the] nucleic acid present in the specimen to obtain extracted nucleic acid, and detecting the presence of the target neoplastic nucleic acid in the extracted nucleic acid.

II. REMARKS

Claims 1 to 18 are pending. For the Examiner's convenience, a copy of the claims as they will stand upon entry of the present amendment is attached hereto as Exhibit A.

A. Regarding the Amendments

The specification has been amended to update the status of the priority application. As such, the amendment merely addresses a formality and does not add new matter.

Claim 1 has been amended to more clearly indicate the alternative sources for obtaining a specimen. As such, the amendment merely addresses a formality and does not add new matter.

Claim 1 also has been amended to more clearly indicate that a method of the invention detects a "mutant" target nucleic acid. The amendment is supported, for example, at page 9, lines 9-15, and, therefore, does not add new matter.

Claim 2 has been amended to more clearly distinguish the recited nucleic acids, and to more clearly define the step of "amplifying" the nucleic acid molecule. The amendment merely clarifies the claim language and does not add new matter.

Claims 2 to 6 and 11 have been amended to recite the term "mutant target nucleic acid" so as to correspond to the language of amended claim 1. The amendments merely address a formality and do not add new matter.

Claim 3 has been amended such that the language more closely parallels that of claim 2, from which claim 3 depends. The amendment, which is necessitated by the amendment to claim 2, merely addresses a formality and does not add new matter.

Claim 4 has been amended to more clearly indicate that the mutant target nucleic acid molecule contains a mutation "selected from" the recited alternatives. The amendment merely clarifies the claim by referring only to the species of "mutations" in the alternative, and does not add new matter.

Claim 4 also has been amended to delete reference to comparing the target nucleic acid to a corresponding wild type nucleic acid, since it is well known in the art that a mutation in a gene is identified with respect to the wild type gene. As such, the amendment merely deletes recitation of superfluous language, and does not add new matter.

Claim 6 has been amended to depend from claim 1, and to more clearly indicate that the "mutant target nucleic acid is a tumor suppressor gene" selected from the recited group. The amendment is supported by the language of previously pending claims 1 and 5 and, therefore, does not add new matter.

Claims 7 to 10 have been amended to insert the term "neoplasm" so as to more clearly define the claimed subject matter. The amendment does not add new matter.

Claim 11 has been amended to more clearly set forth the step of "cloning" the amplified nucleic acid. The amendment merely clarifies the claim language, and does not add new matter.

Claims 12 and 18 have been amended to more clearly indicate that a neoplastic nucleic acid detected according to a method of the invention is one "having a mutant nucleotide sequence." The amendments are supported, for example, at page 8, lines 2-8, and, therefore, do not add new matter.

Claim 12 also has been amended to more clearly indicate that an oligonucleotide useful in a method of the invention is one that "specifically hybridizes" to a neoplastic nucleic acid. The amendment is supported, for example, at page 21, lines 9-14, and at page 45, lines 1-3, and, therefore, does not add new matter.

Claim 17 has been amended to insert the term "acid", which inadvertently was omitted from the claim language. The amendment merely corrects a typographical error and does not add new matter.

Claim 18 also has been amended to more clearly distinguish the "extracted nucleic acid" from the "target neoplastic nucleic acid." The amendment merely clarifies the claim language and does not add new matter.

B. Regarding the Priority

It is requested in the Office Action that reference to the priority application in the specification, be updated to reflect issuance of the parent application. The specification has been so amended and, therefore, it is respectfully requested that this objection be withdrawn.

C. Rejections under 35 U.S.C. §112

The rejections of claims 1 to 18 under 35 U.S.C. §112, second paragraph, as allegedly indefinite are respectfully traversed.

Claims 1 to 11 are rejected as allegedly improperly reciting alternative elements of the claims. Claims 1 and 4 have been amended to address this matter and, therefore, it is respectfully requested that this ground of rejection be removed.

It is alleged that claims 2, 3 and 11 are indefinite in reciting the steps of amplifying or cloning, as it is unclear whether the language is directed to additional steps. The claims have been amended to clarify this matter and, therefore, it is respectfully requested that this ground of rejection be removed.

It is alleged that claim 4 is indefinite in reciting the term "corresponding" in referring to a wild type nucleic acid with respect to a target nucleic acid. Applicants submit, however that one skilled in the art clearly would understand the meaning of the term, since it is well known that a mutation in a nucleic acid sequence is identified by comparison to the corresponding wild type (i.e., non-mutated) nucleic acid. Nevertheless, the term has been deleted from claim 4 as unnecessary and inherent to the claimed method. Accordingly, it is submitted that the rejection is moot.

It is alleged that claim 5 is indefinite in referring to only one of the alternatives of claim 5, from which claim 6 depends. Claim 6 has been amended to depend from claim 1 and to more clearly indicate that the "mutant target nucleic acid" of claim 1 is a tumor suppressor gene as recited. In view of the amendment, it is respectfully requested that this ground of rejection be removed.

It is alleged that claims 12 to 17 are indefinite in reciting the term "preferentially hybridizes" as the term is not provide in the specification and does not have a well established meaning in the art. It is submitted, however, that the term "preferentially" has a commonly understood meaning such that one skilled in the art, reading the claims and having knowledge of nucleic acid hybridization, would know that an oligonucleotide useful in the claimed method hybridizes more specifically to a neoplastic nucleic acid than to a corresponding wild type nucleic acid. Nevertheless, claim 12 has been amended to delete the term "preferentially" and insert therefor "specifically." It is submitted that one skilled in the art would know the subject matter encompassed within amended claim 12 and, therefore, respectfully requested that this ground of rejection be removed.

It is further alleged that claims 12 to 18 are indefinite in reciting the term "neoplastic nucleic acid." More specifically, it is alleged that the disclosure in the specification that a neoplastic nucleic acid is "directly or indirectly associated with a neoplasm" is unclear because it would not be known what is encompassed by the term "associated." Applicants respectfully disagree that the one skilled in the art would not know what it means that a neoplastic nucleic acid is one that is "directly or indirectly associated with a neoplasm." First, it is submitted that the term "associated" is used with respect to its commonly understood meaning, for example, connected together (see Webster's II New College Dictionary, page 68, a copy of which is attached hereto as Exhibit B). Thus, based on the plain meaning of the terms, one skilled in the art would know that a nucleic acid associated with a neoplasm is one in which there is connection between the presence of the nucleic acid and the occurrence of a neoplasm.

Second, the claims have been amended to more clearly indicate that a "neoplastic nucleic acid" detected according to a method of the invention is one "having a mutant nucleotide sequence." As such, it is submitted that the skilled artisan clearly would be apprised of a

neoplastic nucleic acid based on a comparison of the sequence to that of a corresponding wild type nucleic acid.

Third, Applicants point out that the specification generally discloses examples of such neoplastic nucleic acids, including oncogenes and tumor suppressor genes (see page 9, lines 22-28), and also provides numerous specific examples of such neoplastic nucleic acids (see page 10, lines 1-5, and page 6, Table 1). Thus, in view of the specification, the skilled artisan clearly would be apprised of numerous neoplastic nucleic acids, which are known to be directly or indirectly associated with a neoplasm. Accordingly, in view of the plain meaning of the terms used in the claims and in the specification, and further in view of the numerous examples provided in the specification, it is submitted that the skilled artisan clearly would know the metes and bounds of the subject matter encompassed within claims 12 to 18 and, therefore, respectfully requested that this ground of rejection be removed.

Claim 17 is rejected as lacking antecedent basis. The claim has been amended to address this matter and, therefore, it is submitted that this rejection is moot.

It is alleged that claim 18 is indefinite in that it is unclear what "nucleic acid" is being referred to. Claim 18 has been amended to more clearly distinguish the recited nucleic acids. In view of the amendment, it is respectfully requested that this ground of rejection be removed.

For the reasons set forth above, it is submitted that the claims as amended clearly define the subject matter regarded as the invention. Accordingly, it is respectfully requested that the rejections of claims 1 to 18 under 35 U.S.C. §112, second paragraph, be removed.

D. Prior Art Rejections

The rejection of claims 1 to 3, 5, 10, 12 to 14, 17 and 18 under 35 U.S.C. §102(e) as allegedly lacking novelty in view of Sobol et al. (U.S. Pat. No. 5,543,296) is respectfully traversed.

The present invention is directed to a method of detecting a mutant nucleic acid. It is stated in the Office Action that Sobol et al. describe methods for detecting carcinoma metastases by extracting nucleic acids from a sample and detecting a carcinoma associated sequence, that their methods, which includes amplifying a target nucleic acid using oligonucleotides that flank the target sequence, are more sensitive than conventional diagnostic methods, and that the methods utilize samples that are "external to a primary neoplasm." However, Sobol et al. do not teach or suggest detecting a mutant target nucleic acid, or a neoplastic nucleic acid having a mutant nucleotide sequence as required by the claims.

Sobol et al. describe detecting the expression of nucleic acids in tissues (or fluids) that do not normally express the genes (see column 4, lines 45-65). Such "carcinoma associated sequences" are exemplified by numerous well known genes that are normally expressed in various tissues (see column 11, line 13, to column 12, line 33; see, also, Table 1, columns 11-14). Significantly, Sobol et al. do not teach or suggest that the carcinoma associated sequences are mutant nucleic acid sequences. Instead, the method of Sobol et al. is based on the identification of a normal sequence that is expressed in a tumor cell type, for example a lung tumor cell, also being expressed in a tissue or fluid to which tumor cells have metastasized, wherein the tissue or fluid normally does not express the sequence. Sobol et al. report that neurophysin II (Neuro II) and calcitonin gene-related protein (GRP) nucleic acids are present in the bone marrow of cervical cancer patients, but not in bone marrow of normal individuals or of patients with acute ALL (Example 5, columns 20-22). Thus, the reference describes the identification of a normal

gene product in an "abnormal" location in the body, the presence of the gene product indicating that cells of a tumor have metastasized to the body location.

In summary, Sobol et al. do not teach or suggest detecting a mutant target nucleic acid, or a neoplastic nucleic acid having a mutant nucleotide sequence, as claimed, and, therefore, does not defeat the novelty of the claimed invention. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. §102(e) be removed.

The rejection of claims 4 to 6, 15 and 16 under 35 U.S.C. §103(a) as allegedly obvious over Sobol et al. in view of Effert et al. is respectfully traversed.

Sobol et al. is applied as describing methods for detecting carcinoma metastases by extracting nucleic acids from a sample and detecting a carcinoma associated sequence. However, as discussed above, Sobol et al. do not teach or suggest detecting a mutant target nucleic acid, or a neoplastic nucleic acid having a mutant nucleotide sequence as required by the claims. It is stated in the Office Action that Sobol et al. teach a variety of targets that may be analyzed, and acknowledged that Sobol et al. do not teach or suggest using their methods to detect, for example, a mutant nucleic acid sequence such as a mutant tumor suppressor gene.

Effert et al. is applied as describing that p53 mutations are the most common single point mutations associated with cancer cells, and can be detected in primary tumors and in samples from sites of metastases, including lymph nodes. It is alleged that it would have been *prima facie* obvious to modify the method of Sobol et al. to detect p53 mutations as described by Effert et al., for example, in histologically normal lymph node tissues from prostate cancer patients. The motivation to combine the references is alleged to be based on the reference by Effert et al. that mutations in metastatic sites may play a role in the progression of human prostate cancer,

and the reference by Sobol et al. that their methods can detect metastases in tissues that appear normal histologically.

Applicants submit, however, that there is nothing in the Sobol et al. reference relating to the detection of mutant nucleic acid sequences such as a mutant p53 nucleic acid. Instead, the basis of the Sobol et al. reference is that metastases are identified by the expression of an otherwise normal gene product in an abnormal location. Sobol et al. specifically indicate that "[i]n contrast to prior methods for cancer detection, the target nucleic acid is not necessarily an oncogene mRNA product." (column 4, lines 27-30). Thus, absent Applicants' disclosure, one of ordinary skill in the art would not have been motivated to use the method of Sobol et al. to detect a mutant nucleic acid as suggested by Effert et al. because Sobol et al. specifically disclose the detection of otherwise normal gene products "in contrast to prior methods for cancer detection." Accordingly, it is submitted that the claimed invention would not have been obvious over Sobol et al. in view of Effert et al. and, therefore, respectfully requested that the rejection of claims 4 to 6, 15 and 16 under 35 U.S.C. §103(a) be removed.

The rejection of claims 7 to 9 under 35 U.S.C. §103(a) as allegedly obvious over Sobol et al. in view of McAnalley (U.S. Pat. No. 5,587,364) is respectfully traversed.

Sobol et al. is applied as describing methods for detecting carcinoma metastases by extracting nucleic acids from a sample and detecting a carcinoma associated sequence. However, as discussed above, Sobol et al. do not teach or suggest detecting a mutant target nucleic acid, or a neoplastic nucleic acid having a mutant nucleotide sequence as required by the claims.

It is acknowledged in the Office Action that Sobol et al. do not teach or suggest detecting cancer associated sequences associated with benign neoplasms or with head or neck neoplasms.

McAnalley et al. is applied as describing a variety of tumor types, including benign neoplasms and malignant neoplasms of the head and neck. It is alleged that, in view of such teachings, it would have been *prima facie* obvious to modify the method of Sobol et al. to detect nucleic acid targets associated with such neoplasms. However, as discussed above, Sobol et al. do not teach or suggest detecting a mutant target nucleic acid and McAnalley et al. do not provide the teaching necessary for one of ordinary skill to so modify the method of Sobol et al. Accordingly, it is submitted that the claimed invention would not have been obvious over Sobol et al. in view of McAnalley et al. and, therefore, respectfully requested that the rejection of claims 7 to 9 under 35 U.S.C. §103(a) be removed.

The rejection of claim 11 under 35 U.S.C. §103(a) as allegedly obvious over Sobol et al. in view of Mullis et al. (U.S. Pat. No. 4,683,195) is respectfully traversed.

Sobol et al. is applied as describing methods for detecting carcinoma metastases by extracting nucleic acids from a sample and detecting a carcinoma associated sequence. However, as discussed above, Sobol et al. do not teach or suggest detecting a mutant target nucleic acid, or a neoplastic nucleic acid having a mutant nucleotide sequence as required by the claims.

It is acknowledged that Sobol et al. do not teach or suggest cloning amplified nucleic acids prior to detection. Mullis et al. is applied as teaching such cloning of an amplification product. However, Mullis et al. do not teach or suggest a reason for one of ordinary skill in the art to modify the method of Sobol et al. such that the method would be used for detecting a mutant target nucleic acid. Accordingly, it is submitted that the claimed invention would not have been obvious over Sobol et al. in view of Mullis et al. and, therefore, respectfully requested that the rejection of the claim 11 under 35 U.S.C. §103(a) be removed.

III. CONCLUSION

In view of the amendments and the reasons set forth above, Applicants submit that the claims are in condition for allowance and respectfully request that the Examiner issue a notice to that effect. The Examiner is invited to contact the undersigned if there are any questions relating to the subject application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: 12/21/00

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Enclosure: Exhibits A and B